



INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation

Journal Home Page: <https://ijrps.com>

Formulation and evaluation of lyophilized wafers of rizatriptan benzoate

Akshata Shirodker*, Rajashree Gude, Danira Fernandes, Shraddha Bhangle, Steffi Parab, Nidhi Gad, Ankita Verekar

Department of Pharmaceutics, Goa College of Pharmacy, 18th June Road, Panaji Goa, India

Article History:

Received on: 06.04.2018

Revised on: 21.06.2018

Accepted on: 26.06.2018

Keywords:

Wafer,
Freeze-drying,
Rizatriptan benzoate,
Hydrophilic polymers

ABSTRACT

Migraine is a headache of varying intensity often accompanied by nausea and sensitivity to light and sun. The present investigation deals with the formulation and evaluation of oral wafer of rizatriptan benzoate which is used for the treatment of migraine. The wafer formulation was prepared by freeze-drying an aqueous solution of rizatriptan benzoate containing various hydrophilic polymers like hydroxypropyl methylcellulose E3, hydroxypropyl cellulose EF, maltodextrin and polyvinyl alcohol as matrix formers. The formulations were evaluated for parameters like physicochemical properties, compatibility, glass-transition temperature, *in vitro* release, and stability. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy and differential scanning calorimetry. The results revealed no physical and chemical incompatibility between the drug and the excipients employed. The prepared formulations were evaluated for different physicochemical properties like appearance, thickness, weight variation, friability, loss on drying, drug content, disintegration time and wetting volume. Scanning electron microscopy studies were carried out on the optimized formulations to study the internal structure of the lyophilized wafer systems. *In vitro* release data showed that more than 90% of the drug dissolved within 5 min. All formulations were found to be stable after doing one-month stability studies under accelerated conditions (40°C and 75% relative humidity) without significant alteration in physical appearance and drug content. It was concluded that formulations containing hydroxypropyl methylcellulose E3 produced optimized results.



* Corresponding Author

Name: Akshata Shirodker

Phone: +91-9637909477

Email: shirodkerakshata@gmail.com

ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v9i4.1644>

Production and Hosted by

IJRPS | <https://ijrps.com>

© 2018 | All rights reserved.

INTRODUCTION

Contract manufacturing organizations often champion new drug-delivery technologies. Such a technology evolution has been evident for orally disintegrating wafers (ODWs) (McLaughlin R *et al.*, 2009) The ultimate aim of any prescribed medical therapy is to achieve certain desired outcomes in

the patients concerned (Jin *et al.*, 2008). Fast dissolving dosage forms play an important role in developing effective medication for specific patient groups which include pediatrics, the elderly, other groups with conditions such as dysphagia, nausea and/or vomiting, as well as patients on antipsychotic drugs. Fast dissolve formulations also bring significant benefits in the convenience of 'on-the-go' medications, for indications and ailments which have unpredictable occurrence but a rapid onset, such as migraine or diarrhea (Travers *et al.*, 2013).

Migraine is a genetically influenced chronic brain condition marked by paroxysmal attacks of moderate-to-severe, throbbing headache with associated symptoms that may include nausea, vomiting, and photophobia or phonophobia (Loder E. *et al.*, 2010). Traditional tablets and capsules administered with 250 ml of water may be inconvenient for pediatric, geriatric, bedridden, nauseous or non-

Table 1: Composition of lyophilized wafers of rizatriptan benzoate

Ingredients	Quantity present in the solution to be lyophilized							
	F1	F2	F3	F4	F5	F6	F7	F8
Rizatriptan Benzoate (mg)	7.265	7.265	7.265	7.265	7.265	7.265	7.265	7.265
HPMC E3 (%)	1	2.5	---	---	---	---	---	---
HPC EF (%)	---	---	1	2.5	---	---	---	---
Maltodextrin (%)	---	---	---	---	1	2.5	---	---
PVA (%)	---	---	---	---	---	---	1	2.5
Mannitol (%)	3	3	3	3	3	3	3	3
Glycine (%)	1	1	1	1	1	1	1	1
Aspartame (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Peppermint flavour (%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

compliant patients. Hence formulating an antimigraine drug as lyophilized wafers would be the perfect alternative thus offering an advantage of the convenience of administration, e.g. while travelling when there may not be easy access to water. Rizatriptan benzoate - a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist - was chosen as the model drug.

MATERIALS AND METHODS

Rizatriptan benzoate was supplied by Glenmark Generics Ltd., Colvale, Goa. Hydroxypropyl methylcellulose E3 (HPMC E3) was obtained from Colorcon Asia Pvt. Ltd., Verna, Goa. Hydroxypropyl cellulose EF (HPC EF) was supplied by Unichem Laboratories Ltd., Pilerne, Goa. Maltodextrin was purchased from HiMedia Laboratories Pvt. Ltd. Polyvinyl alcohol (PVA) was obtained from Thomas Baker. The water used was deionized water. All other chemicals used were of laboratory grade and used as received.

Standardization of rizatriptan benzoate

The standard curve for rizatriptan benzoate was obtained by first preparing a 10 µg/ml stock solution of the drug in deionized water at 224.20 nm using UV spectrophotometer (Lab India). From this, a series of dilutions were made in deionized water to obtain a concentration range of 1-8 µg/ml.

Preformulation studies- Compatibility study

Infrared (IR) spectroscopy

Fourier transforms infrared (FTIR) spectra of the individual drug and physical mixtures of drug and the excipients (1:1) prepared in KBr disc was obtained using IR-spectrophotometer (Shimadzu) scanned over 400 to 4000 cm⁻¹.

Drug-polymer interaction studies

Differential scanning calorimetry (DSC) was used to characterize thermal properties of rizatriptan benzoate and physical mixtures of the drug and polymer in the ratio 1:1. The DSC thermograms were recorded using Pyris 1 (Perkin Elmer, USA).

The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min over the temperature range of 30°C to 300°C.

Glass transition

DSC (Mettler Toledo) was used to determine the glass transition temperature (T_g) and thermal properties of the formulation in their frozen state (before freeze-drying). 5-15 mg of the liquid sample of the formulation was loaded into aluminum pans, cooled from 20°C to -60°C at a rate of 10°C/min and the resulting thermogram was analyzed (Patra M. *et al.* 2013).

Formulation of wafers (freeze-drying method)

Rizatriptan Benzoate wafer was prepared by freeze-drying an aqueous solution of HPMC E3, HPC EF, maltodextrin and PVA as matrix forming agents, mannitol (filler), glycine (anti-collapsing agent), aspartame (sweetener) and peppermint flavour (flavouring agent). The drug and the rest of the excipients were first dissolved in a sufficient quantity of deionized water using a magnetic stirrer to obtain a homogenous solution. This was then made up with water (quantity sufficient). While preparing solutions containing PVA, the water was heated to about 80°C to aid in the rapid formation of a solution. The resulting solution was transferred by pipette and accurately weighed into preformed blister pack wells, resulting in a rizatriptan dose of 5 mg per wafer, before freezing in the freeze-dryer (Lyolab) at -40°C for approximately 5.5 h. Primary drying was conducted at -20°C for 34 h. Finally, the shelf inlet temperature was ramped to 25°C and maintained for additional time for secondary drying. The blister packs containing the lyophilized wafers were then removed and then heat-sealed using a blister packing machine (Ezee-Blist, Mechtek) with aluminum foil at 119.5°C to get a peelable lidding foil. The composition of lyophilized wafers of rizatriptan benzoate is given in Table 1.

Evaluation of lyophilized wafers

Visual inspection of wafers

Morphological characterization of the freeze-dried wafers comprised of shape, colour and surface. Adhesion of the wafers to the blister and the ease of taking them out were also evaluated.

Thickness

The thickness of five wafers from each formulation was determined using a Vernier calliper (Mitutoyo, F.M. Instrumentation, Japan), and average values were calculated.

Weight variation

Twenty wafers were selected randomly and the average wafer weight was calculated. All the wafers were made sure to not deviate from the average weight by more than $\pm 10\%$.

Friability

The friability of the lyophilized wafer was determined using the Roche friabilator (Veego). Ten wafers were initially weighed ($W_{initial}$) and transferred into the friabilator, operated at 25 rpm for 4 min. The wafers were then reweighed W_{final} .

$$F = \frac{W_{final} - W_{initial}}{W_{initial}} \times 100$$

In vitro disintegration time

A Petri dish (10 cm diameter) was filled with 10 ml of water. The wafer was carefully put in the centre of Petri dish and the time for the wafer to completely disintegrate into fine particles was noted (Mangal M. *et al.*, 2012).

Moisture content

The moisture content of the wafer was determined using Halogen moisture analyzer (MA-150C/Sartorius) with 2.0 g of crushed wafer matrix at 105°C for 5 min. The reading obtained was the % loss on drying.

Wetting volume

The wafer is placed in the centre of the Petri dish and with the help of 5 ml pipette; distilled water was added dropwise on the wafer. The volume required to disintegrate the wafer completely was noticed as the wetting volume (Parthiban *et al.*, 2013).

Uniformity of content

A wafer was weighed and dissolved in about 70 ml of deionized water taken in a 100 ml volumetric flask. The flask was shaken for ten minutes and made up to the 100 ml mark. After shaking for two minutes, the solution was filtered; rejecting the first few ml of the filtrate. 5 ml of the filtrate was

transferred to a 25 ml volumetric flask and diluted up to the mark with deionized water. 1 ml of the resulting solution was transferred to a 10 ml volumetric flask and diluted up to the mark with deionized water. The absorbance of this solution at 224.20 nm was recorded. The concentration of rizatriptan benzoate in $\mu\text{g/ml}$ was calculated. Drug content studies were calculated in triplicate for each formulation batch.

Rizatriptan content in mg was calculated using the formula:

$$= \frac{\text{concentration in } \mu\text{g/ml}}{1000} \times 100 \times \frac{25}{5} \times \frac{10}{1} \times \frac{269.44}{391.5}$$

Drug content claim was 5 mg of rizatriptan.

Assay

Twenty wafers were dissolved in a 100 ml volumetric flask with deionized water. The solution was filtered and 6.82 ml (which is equivalent to 10 mg of rizatriptan benzoate) of the filtrate was transferred to a 100 ml volumetric flask and diluted to 100 ml mark with water to give a solution of 100 $\mu\text{g/ml}$. 0.5 ml of this solution was then taken in a 10 ml volumetric flask and made up to mark. The absorbance of the solution was recorded at 224.20 nm and the concentration of rizatriptan was calculated.

In vitro dissolution studies

The dissolution studies on the fast dissolving lyophilized wafers were performed using USP II paddle apparatus. The wafers were introduced in the dissolution vessel containing 900 ml of deionized water, thermostated at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. The stirrer depth was set at 25 mm. Five ml of the dissolution fluid was withdrawn by the autosampler after every 5 min, for 15 min. The volume withdrawn at each time interval was replaced by a fresh quantity of dissolution fluid. The samples were filtered automatically and analyzed manually by UV spectrophotometer at 224.20 nm. The average of 3 readings was taken (Parthiban *et al.*, 2013).

Scanning electron microscopy

The cross-section of F1 and F2 were examined by scanning electron microscope (Carl-Zeiss, India). Cross-section of the samples was prepared by cutting a thin slice of the wafer using a scalpel. Samples were placed on a brass stub using adhesive tape. SEM images were recorded at an acceleration voltage of 20 kV.

Accelerated stability studies

Stability studies were carried out on optimized formulations (F1, F2, and F7) according to International Conference on Harmonization (ICH) guidelines. The sealed PVC-aluminum blisters containing the best two formulations were wrapped in aluminum foil, and then further sealed in polybags and subjected to accelerated stability testing in a photostability chamber (Osworld) for 1 month at a temperature $40 \pm 2^\circ\text{C}$ and relative humidity $75 \pm 5\%$. Samples were taken at 30 d and analyzed for the change in physical appearance and drug content by procedures stated earlier. Tests were carried out in triplicate and mean of the observed values was noted.

RESULTS AND DISCUSSION

Standardization of rizatriptan benzoate

Calibration curve of rizatriptan benzoate was obtained by plotting a graph of absorbance v/s concentration. Spectrophotometric data for construction of calibration curve is given in Table 2. Fig. 1 shows the calibration curve of rizatriptan benzoate in deionized water. The linearity of rizatriptan benzoate as obtained from the calibration curve was found in the concentration range of 1-8 $\mu\text{g/ml}$.

Table 2: Spectrophotometric data for construction of calibration curve of rizatriptan benzoate in deionized water

Concentration ($\mu\text{g/ml}$)	Absorbance at 224.20 nm
1	0.139
2	0.233
3	0.413
4	0.543
5	0.673
6	0.786
7	0.918
8	1.040

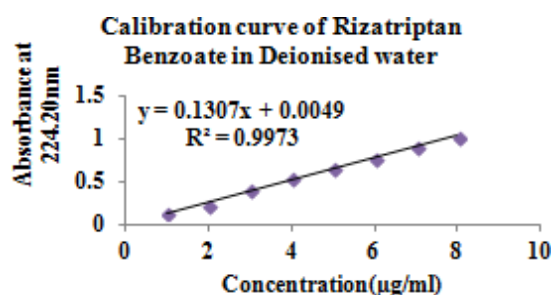


Figure 1: Calibration curve of rizatriptan benzoate in deionized water

Preformulation study- Compatibility studies

Infrared (IR) spectroscopy

Substantial changes in IR absorption bands were not observed for the drug in the physical mixture.

FTIR spectra of the drug and its physical mixture with HPMC E3 are shown in fig. 2 and 3 respectively.

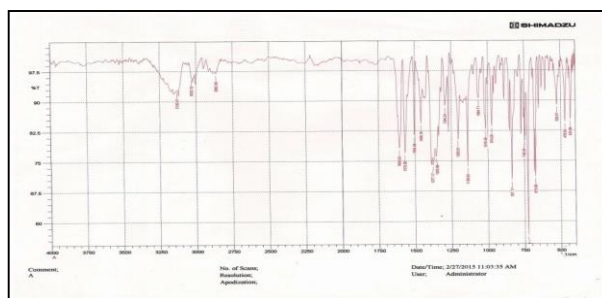


Figure 2: FTIR spectra of rizatriptan benzoate

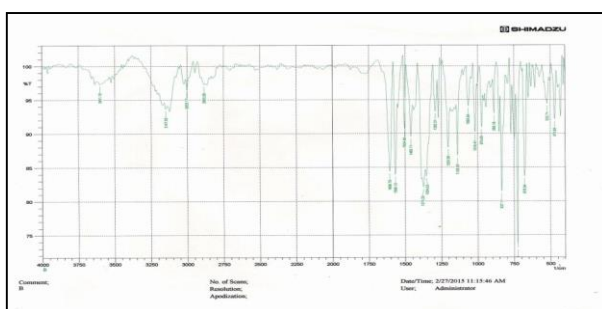


Figure 3: FTIR spectra of rizatriptan benzoate and HPMC E3

Drug-polymer interaction studies

DSC thermograms revealed that there is no considerable change observed in melting peak of rizatriptan benzoate pure drug (182.77°C) and drug with the polymers which indicates that no interaction takes place between drug and the polymers used in the formulation. The thermogram of pure drug rizatriptan benzoate and physical mixture of the drug with HPMC E3 is shown in fig. 4 and 5 respectively. IR spectrometry studies and DSC studies of rizatriptan benzoate and its mixtures showed that the drug is compatible with the excipients used in the design of the lyophilized wafers of rizatriptan benzoate.

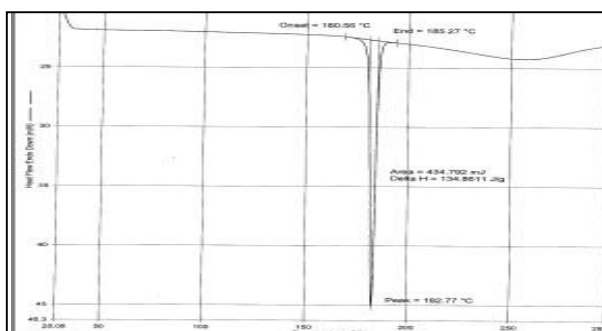


Figure 4: DSC profile for rizatriptan benzoate

Table 3: Glass-transition temperature of samples

Formulation	T_g ($^\circ\text{C}$)
F1	-8
F3	-7
F5	-7
F7	-9

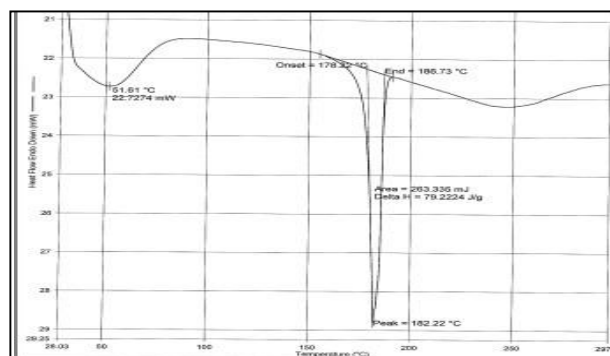


Figure 5: DSC profile for a physical mixture of rizatriptan benzoate and HPMC E3 (1:1)

Glass transition

The T_g values for the solutions analyzed are tabulated in Table 3. Solutions of the formulations to be lyophilized (F1, F3, F5, F7) were used to determine the T_g

Evaluation of wafers

Visual inspection of wafers

The visual characteristics of the wafers and their ease of removal from the blisters are summarized in Table 4. The wafers were round in shape and white to off-white.

Thickness: The Thickness of the wafers is reported in Table 5. The thickness evaluation revealed that the variations in thickness among the formulations might be the consequence of the difference in molecular weight and the concentration of polymer used.

Weight variation

The weight of wafers from each formulation is summarized in Table 5. The variations in weight among the formulations may be the consequence of the difference in molecular weight and the concentration of polymer used.

Friability

The friability of wafers for each formulation is reported in Table 5. Friability studies show acceptable percentage weight loss, within the acceptable range (less than 1%) except F5 which contains Maltodextrin. From the friability studies, though the wafers showed acceptable friability, they were soft with a spongy consistency and would deform on rough handling. However, the PVC blister packs used, confer both strength and protection to the product and can be considered as an integral part of the product. The *in situ* freeze-drying process results in a slight degree of adhesion between the dried product and surface of the laminate and this ensures that the formulation remains fixed in the blister pocket until it is removed immediately before administration. This adhesion, and the natural "perfect fit" of the dose in the blister cavity, also

means that the product cannot move around within the pocket, so it cannot be abraded through handling or transportation (Kearney *et al.*, 2013). It was seen that higher the concentration of the matrix-former (F1 v/s F2) and (F3 v/s F4), the lesser is the friability. It has been reported that increasing the matrix former concentration usually results in a more extensive and rigid 3D network after freeze-drying due to increase in the number of matrix fibres forming crosslinks and interchain H-bonds, thereby resulting in a decrease in the friability of wafers (El Degwy *et al.*, 2012).

Table 4: Visual inspection of wafers

Formulation	Surface of wafers	Durability of wafers	Removal from the blisters
F1	Porous	Durable	+
F2	Porous	Durable	+
F3	Porous	Durable	+
F4	Porous	Durable	+
F5	Porous	Highly fragile	-
F6	Porous	Highly fragile	-
F7	Porous	Durable	+
F8	Porous	---	-

(+) The tablet can be easily taken out from the blister; (-) the tablet sticks to the blister and/or cannot be removed without damage

In vitro disintegration time

The disintegration time of each formulation is reported in Table 6. It was noted that increasing polymer concentration resulted in an increase in wafer disintegration time, which can be attributed to the formation of a more extensive wafer binder matrix. The type of polymer used in the formulation influence the disintegration profile of the formulations. Fastest disintegration profile was seen in case of HPMC E3 while the disintegration rate of wafers containing HPC EF was the least. The reason for spontaneous disintegration seen in most of the formulations was due to the characteristically high porosity produced by the freeze-drying process used in its manufacture. The highly porous structure allows the rapid ingress of water, which quickly dissolves the soluble excipients, releasing the drug particle as a suspension or solution on the tongue (Kearney *P et al.*, 2002).

Moisture content

The moisture content of wafers for each formulation is summarized in Table 6. Unlike other freeze-drying processes, e.g. for parenteral, the drying cycle does not determine the final residual moisture content of the product. Moisture levels of 2% w/w are typically achieved at the end of the cycle, but once the product is removed from the dryer it quickly reabsorbs water from the

Table 5: Evaluation of wafer: thickness, weight variation, wetting volume and friability

F. code	Thickness (mm)	Weight variation (mg)	Wetting volume (ml)	Friability (%)
F1	6.73±0.04	54.3±0.56	0.05	0.92
F2	7.03±0.03	73.83±1.35	0.15	0.14
F3	6.36±0.02	55.2±0.42	0.45	0.27
F4	6.3±0.04	71.95±0.57	1.2	0.21
F5	6.53±0.44	53.25±0.76	0.05	23.64
F6	-	-	-	-
F7	6.53±0.05	56.13±1.92	0.1	0.72
F8	-	-	-	-

Table 6: Evaluation of wafer: in vitro disintegration time, LOD, uniformity of content, assay

Formulation code	<i>In vitro</i> disintegration time (s)	LOD %w/w	The content of rizatriptan in mg	Assay	
				Content of rizatriptan benzoate (%)	Content of rizatriptan (mg/wafer)
F1	1.43±0.046	7.69	4.950	98.154	4.908
F2	1.98±0.04	6.43	4.976	99.846	4.992
F3	41.78±1.46	6.36	4.870	97.538	4.877
F4	103.98±2.46	4.96	4.818	95.538	4.777
F5	1.48±0.036	6.80	4.791	93.538	4.677
F6	-	-	-	-	-
F7	13.46±0.16	6.25	5.003	98.462	4.923
F8	-	-	-	-	-

Table 7: In vitro dissolution data of formulation F1-F8

Formulation	Time (min)	Conc. in µg/5 ml	Conc. in 900 ml mg	Cumulative release	Cumulative % drug release
F1	5	37.385	6.729	6.729	94.369
	10	37.923	6.826	6.864	96.26
	15	39.007	7.034	7.111	99.72
F2	5	39.5	7.11	7.11	98.015
	10	39.923	7.186	7.226	99.615
	15	39.769	7.158	7.238	99.782
F3	5	37.423	6.736	6.736	95.063
	10	37.885	6.819	6.857	96.77
	15	38.346	6.902	6.979	98.483
F4	5	35.769	6.438	6.438	92.76
	10	38.115	6.861	6.899	99.393
	15	37.962	6.883	6.909	99.541
F5	5	37.231	6.702	6.702	98.61
	10	37.192	6.695	6.732	99.055
	15	37	6.66	6.734	99.091
F6	-	-	-	-	-
F7	5	38.538	6.937	6.937	96.979
	10	39.269	7.068	7.108	99.367
	15	39.038	7.027	7.105	99.332
F8	-	-	-	-	-

atmosphere to a level dependent on the nature of the formulation and this can vary from 3 to 8%

w/w. At ambient temperature, the lyophilized matrix can reversibly absorb higher amounts of water without adversely affecting the physical stability of the product (Kearney P *et al.*, 2002).

Wetting volume

The wetting volume is important to check the

minimum volume of water required for wetting of wafer. The data is reported in Table 5. From the wetting volume test, it was observed that wetting is closely related to the inner structure of the wafers and the hydrophobicity of the excipients. Low wetting volume is an indication that a wafer would disintegrate almost instantaneously when it comes in contact with the even slight amount of saliva in the mouth.

Uniformity of content

The results of content uniformity are tabulated in Table 6. The result indicated that the process employed to prepare batches in this study was capable of giving wafers with uniform drug content and minimum batch variability.

Assay

The assay of rizatriptan benzoate was performed using UV spectrophotometer. The limit for the assay was set as follows:

The content of rizatriptan benzoate equivalent to rizatriptan shall be between 90-110% of the label claim. The label claim was 5 mg of rizatriptan. The lower limit was 4.5 mg and the upper limit was 5.5 mg of rizatriptan. The assay results show that the wafers contain rizatriptan benzoate between 93.538-99.846% which was within acceptable limits. Table 6 shows the results of the formulations.

In vitro dissolution studies

The results of *in vitro* dissolution studies are tabulated in Table 7. It was observed that in general, the type of polymer influences the rate of drug release. The percentage of drug dissolved from all the formulations was almost 100% after 15 min. The plot of cumulative % drug released v/s time for formulation F1, F2, F3, F4, F5 and F7 are given in fig. 6. From *in vitro* dissolution studies, it was observed that formulations F3 and F4 containing HPC EF showed a slower rate of drug release initially.

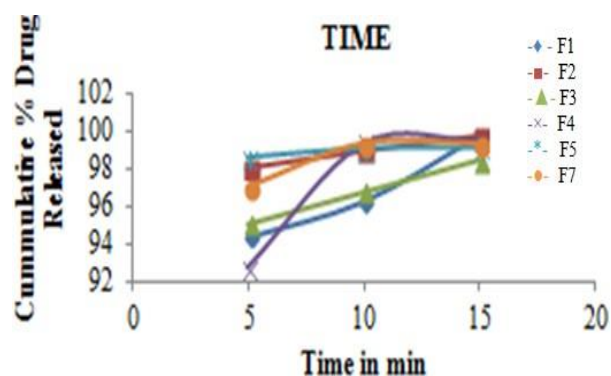


Figure 6: Plot of cumulative % drug released v/s time

Scanning electron microscopy

Scanning electron micrographs of the cross-section views of ODWs (F1 & F2) is shown in fig. 7A and 7B. The micrographs show the highly porous nature of the prepared lyophilized wafers in the inner structure. The highly porous nature of the wafers explains the rapid penetration of water, which results in rapid wetting, disintegration, and dissolution in the oral cavity.

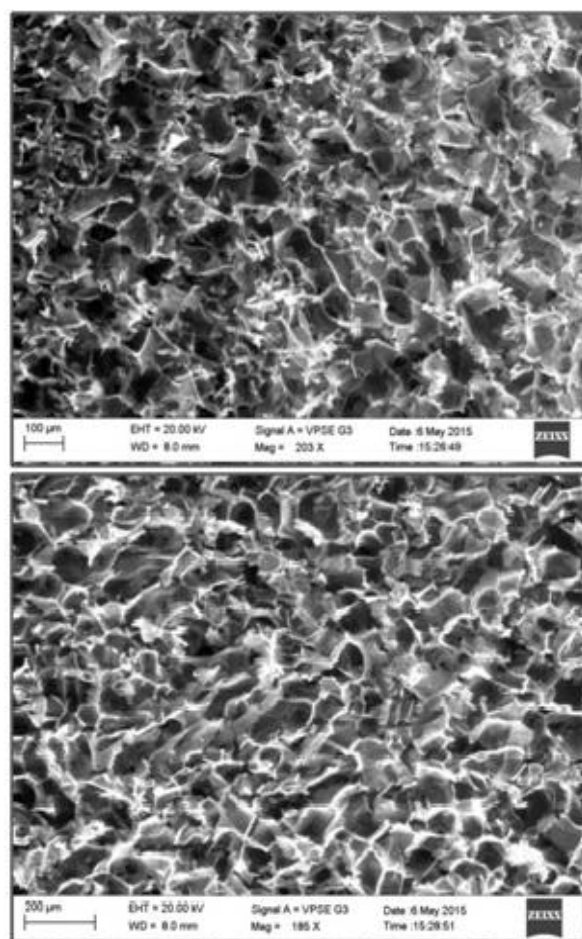


Figure 7: Scanning electron micrograph of a cross-section (A) F1 and (B) F2

Accelerated stability studies

The successful batches of rizatriptan wafers (F1, F2, and F7) were subjected to stability testing at 40°C, 75% RH for 1 month. Their disintegration time and uniformity of content were evaluated and the results are tabulated in Table 8. The results of stability testing indicated that the samples were chemically and physically stable over the tested period.

Table 8: Accelerated stability testing parameters

Formulation	Disintegration time (s)	Drug content (mg)
F1	1.38	4.841
F2	1.95	4.923
F7	14.42	4.976

CONCLUSION

The lyophilized wafer of rizatriptan benzoate developed throughout this research is an effective and versatile drug delivery system in the treatment of migraine. It omits the rate-limiting disintegration step of conventional wafers which would mean a faster release of the drug at the site of absorption.

The designed formulation exhibited excellent

physicochemical properties and dissolution profile (almost 100% *in vitro* release at the end of 15 min) with adequate stability.

This work needs to be proved effective by its bio-availability, preclinical and clinical studies thus providing a platform for further development and optimization.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Acknowledgements

The authors would like to express their heartfelt thanks to the Department of Pharmaceutics, Goa College of Pharmacy, for providing us with valuable information during the experiment. We are grateful to Dr. Nitin Borkar, CEO, VerGo Pharma Research, Verna- Goa, for granting permission to work on the premises and avail of all other facilities.

REFERENCES

- El Degwy MAAEAA, Tayel S, El-Nabarawi MA, Rehem RTA. *In vitro* and *in vivo* evaluation of aceclofenac lyophilized orally disintegrating wafers. *Int J Pharm Sci Res* 2012;3:443-59.
- Jin J, Sklar GE, Oh VMS, Li SC. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag* 2008;4:269-86.
- Kearney P. The Zydis Oral fast dissolving dosage form. Rathbone MJ, Hadgraft J, Roberts MS, editors. *Modified-Release Drug Delivery Technology*. New York: CRC Press; 2002, p. 191-202.
- Loder E. Triptan therapy in migraine. *N Engl J Med*. 2010;363:63-70.
- Mangal M, Thakral S, Goswami M, Thakur N. Comparison study between various reported disintegrating methods for fast dissolving wafers. *African J Basic Appl Sci* 2012;4:106-9.
- McLaughlin R, Banbury S, Crowley K. Orally disintegrating wafers-the effect of recent FDA guidance on ODW technologies and applications. *Pharm Technology*. 2009;33.
- Parthiban KG, Kumar MP. Formulation and evaluation of oral dispersible wafers of rizatriptan benzoate. *IJCPR*. 2013;5:31-5.
- Patra M, Acharya PK, Seth S, Shadangi M. Differential Scanning Calorimetry (DSC) an Essential and Critical Instrument in Optimizing Lyophilization Process. *International Journal of Life sciences Pharma Reseach*. 2013; 3(4):11-19.

Travers R, Grother L. Fast dissolved formulations. *PMPS*. 2013:44-7.